Cage-modified hypocrellin against multidrug-resistant *Candida* spp. with unprecedented activity in light-triggered combinational photodynamic therapy

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1、簡述論文的概要與重大發現

由多重耐藥真菌引起的感染對全球人類健康構成毀滅性威脅，迫切需要新的抗真菌策略。抗菌光動力療法 (aPDT) 由於其在對抗真菌感染方面的潛力而受到越來越多的關注，而要製備高效水溶性光敏劑（PS）仍然是一個挑戰。所以作者就引入多孔籠化合物來製備用於高效 aPDT 的強大 PS，這可以促進 O_2 和活性氧 (ROS) 的運輸，利用天然 PS hypocrellin A (HA) 連接到具有聚乙二醇 (PEG) 鏈的新型有機籠狀化合物（共價有機多面體 1 結合，COP1T）以提高其水溶性。製備的 COP1T-HA 顯示出良好的生物相容性、低暗毒性和提高的成纖維細胞和角質形成細胞的遷移能力，以及對多重耐藥真菌浮游細胞和生物膜的抗真菌活性。同時，體內和體外實驗證明 COP1T-HA 具有出色的抗真菌性能和傷口癒合能力，具有良好的生物安全性，顯示出巨大的生物醫學應用潛力。

2、對論文內容的疑問

在 Fig.7C 中，Periodic Acid Schiff (PAS)染色會將真菌微生物染成紫　色，但圖片中並沒有很明顯地顯示出，所以無法證明 *C. albicans* 的存活率是否有變少?

3、論文的缺點與評論

作者利用 Porous Organic Cages(POCs)的 COP1T 與光敏劑 HA 組合出新的組合 COP1T-HA，而隨著進一步的開發和優化，有很大的潛力成為一類新的抗真菌劑來對抗耐藥病原體。

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ABSTRACT

Infections caused by multidrug-resistant fungi pose a devastating threat to human health worldwide, making new antifungal strategies urgently desired. Antimicrobial photodynamic therapy (aPDT) has gained increasing attention due to its potential in fighting against fungal infection. However, the preparation of highly efficient and water-soluble photosensitizers (PSs) for this purpose remains a challenge. Herein, we present a new strategy to prepare powerful PSs for efficient aPDT by introducing a porous cage compound, which could facilitate the transportation of O_2 and reactive oxygen species (ROS). Specifically, the natural PS hypocrellin A (HA) was attached to a novel organic cage compound (covalent organic polyhedra 1 tied, COP1T) with polyethylene glycol (PEG) chains to improve its water solubility. It was found that the resulting COP1T-HA exhibited *in vitro* antifungal efficiency several folds higher compared to the free HA in fighting against four types of multidrug-resistant fungal planktonic cells and biofilms, including the "super fungus" *Candida auris*. Interestingly, the red-shift of COP1T-HA adsorption led to the realization of phototheranostic aPDT for cage-modified HA or derivatives. Additionally, COP1T-HA exhibited good biocompatibility, excellent disinfection capacity and wound healing efficiency without obvious toxic effects *in vivo* of rat model. With further development and optimization, COP1T-HA has great potential to become a new class of antifungal agent to fight against drug-resistant pathogens.

1. Introduction

Human-associated fungal infection has become one of the deadliest threats to global health, killing over 1.5 million people per year worldwide (Bongomin et al., 2017). Additionally, the COVID-19 pandemic brings a huge shock to global healthcare systems, forcing

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